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POTASSIUM KINETICS IN A WHOLE ANIMAL: A THEORETICAL STUDY

Peter Egbert

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POTASSIUM KINETICS IN A WHOLE ANIMAL--

A THEORETICAL STUDY

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ACKNOWLEDGEMENT

I wish to thank Dr. J. A. Stolwijk for his advice concerning this thesis and especially for his help with the computer work involved.

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The intention of this work is to examine theoretical conditions of steady state K^+ kinetics in a whole animal with an attempt to include quantitative as well as qualitative considerations. Experimental, calculated, and when necessary, estimated data are combined into a significantly complete model.

This model consists of several interconnecting compartments representing volumes of distribution of K. The exchange of K between compartments is related by a series of differential equations. An analogue computer is then used to combine the equations and draw a theoretical time-concentration curve which may be compared to an experimentally found time-concentration curve. The computer merely provides a means for manipulation and visualization of otherwise rather cumbersome equations.

This method may give a partial check to the theoretical conditions proposed, if the results from the model agree with the experimental ones. As the computer is more flexible than a real animal, one may also attempt to predict what would happen in untested situations such as changing blood flows or rate constants for K transfer in different compartments. The model may also be able to point to specific gaps in experimental data which are

necessary to understand K distribution, and thereby suggest meaningful experiments. This is perhaps the greatest value of this method of systems analysis--to serve not as an end in itself, but as an aid to further experimentation.

K^{42} is known to disappear very rapidly from arterial plasma after venous injection into whole animals. More than 90% is removed within one minute after injection in dogs(25) and rabbits(37). Black(2) injected K^{42} into humans and found the plasma contained 5% of the initial amount at two minutes and less than 1% at 5 minutes. The rate of disappearance of K^{42} was compared to that of other ions and found to be 1½-2 times that for D_2O and 4-6 times that for $Na^{22/24}$(5,25,31). A proposed reason for this is that the large intracellular pool of K^+ dilutes the tracer more than intracellular H_2O or Na^+(31). Code(5) found injection into the portal vein instead of a peripheral vein quickened the disapperarance slightly. Walker(37) found evisceration of the liver did not change his slope significantly. However, in spite of the rapid initial exchange, the final equilibrium of K^{42} is slow--only 75-95% of total body K^+ is exchangeable in 48 hours.

The different contributions of separate organs to the disappearance of plasma K^{42} has been studied by measuring the radioactivity in different organs at some

time after injection. Ginsburg(13), working with rats, concluded that organs could be separated into rough groups according to their rate of K^{42} uptake during the first few minutes after injection: organs with fast rates--kidney; intermediate rates--liver, gut, skin; slow rates--muscle; very slow rates--brain, erythrocytes, bone. His results agree well with similar studies on rabbits(11,37). Corsa(7) also studied rabbits, but analyzed organs 20-30 hours after injection, finding equivalent specific activities in kidney, liver, muscle, and heart, and lower specific activity in brain, erythrocytes and bone. Black(2) concluded that in general K^{42} distributes in tissues according to blood flow, with the exception of brain and erythrocytes which have a high blood flow and nevertheless a low uptake.

The above studies do not separate the influences of blood flow and cell membrane permeability. The rate of exchange of K across the cell membrane in the steady state has been studied by isolated cell and isolated organ techniques. Work with in vitro amphibian muscle gave the exchange rate as 1.1×10^{-4} meq/gm/min(14), 1.7×10^{-4}meq/gm/min(30), or 9.0×10^{-6}meq/cm^2/min(38). It is interesting to compare this to the cell wall exchange rate for the plant, Chara australis, of

1.2-3.0 x 10^{-7} meq/cm^2/min. These in vitro values nave a variation dependent upon temperature and concentration in the bathing medium Krebs(36) obtained a slow in vitro turnover rate $\left(\frac{\text{K exchanged}}{\text{K in tissue}}\right)$ of .035-.04 for guinea pig brain cortex and .07-.10 for retina.

Conn and Robertson(6) obtained faster exchange rates in an in vivo study of the myocardium of the dog. They adjusted venous infusion of K^{42} so that a constant arterial concentration was maintained, and took samples from a catheter in the coronary sinus. A multiexponential equation was fitted to the time-concentration curve of the coronary sinus blood. From the constants of this equation plus values of interstitial and intracellular K amounts, they were able to calculate rate constants for K transfer from interstitial to intracellular fluid(1.95-4.53 min^{-1}) and from intracellular to interstitial fluid(.036-.061 min^{-1}), and the amount of K exchanged across the cell membrane(3.05-5.00 x 10^{-3}meq/gm of left ventricle/min.) A similar study of brain(20) found diffusion in brain to be much slower--6.0 x 10^{-5}meq/gm/min.

The use of compartmental models in conjunction with tracer experiments has increased in recent years. The complete mathematical description of general two

and three compartment systems has been developed(4,34). Although the physiologic concept of a three compartment system is simple, the calculated solution is not. The theory of expanding a compartmental system with a computer into a more extensive model has been given(15,22), as well as a hydrodynamic model(39). Robertson and Cohn(32) used an analogue computer to represent a four compartment model for strontium and calcium metabolism in man, and were able to estimate turnover rates by fitting the theoretical curve to experimental data. Pace(29) developed a simple analogue computer model for study of water and electrolyte flows in extracellular fluids, but did not have quantitative constants or specific applications. As well as I have been able to determine, no quantitative model of K distribution or kinetics has been proposed.

DESCRIPTION OF THE MODEL

The data which was chosen to work from are that provided by Walker and Wilde(37). They injected about 0.5ml containing 0.15 meq K^{42} into an ear vein of anesthetized rabbits in 3-5 seconds, then took frequent

1ml. carotid artery samples and analyzed the plasma for K^+ and radioactivity. Some animals were killed at 2 minutes after injection and different organ samples were weighed and analyzed for K^+ and radioactivity. This work was selected to provide the basic data for the model because, 1)experimental techniques were acceptable,2) the amount of K^{42} injected was small enough not to disturb the steady state equilibrium of the animals--this was often not true in earlier tracer experiments, 3) it gives many points at which to compare the theoretical model,in the form of an arterial time-concentration curve and several tissue concentrations.

As stated above, the model consists of compartments representing different volumes of distribution of K throughout the body. The compartments used and their connections are diagramed in Fig. 1.

Definition of terms

Compartments:

a = arterial plasma;

vein = venous plasma;

k = kidney;

v = liver and gut;

m = muscle and skin;

r = remaining tissue except lungs and erythrocytes;

i.e., skeleton, CNS, etc. Lungs and erythrocytes are not included in any compartment due to their unique blood flow. Their omission is justified because of their small, albeit rapid, uptake of K^{42}-- only 1.9 and 0.18% of the total at 2 minutes(37);

x.i, x.c = interstitial and cellular compartments of x; x refers to k, v, m, or r.

Concentrations(% of initial venous concentration):

C_a, C_{vein} = concentration of K^{42} in a and vein;

$C_{x.vein}$ = concentration of K^{42} in the venous plasma leaving x;

$C_{vein.0}$ = initial concentration of K^{42} in vein;

$C_{x.i}$, $C_{x.c}$ = concentration of K^{42} in x.i and x.c.

Quantities(% of initial venous concentration times ml.):

Q_a, Q_{vein}, $Q_{x.i}$, $Q_{x.c}$ = quantity of K^{42} in a, vein, x.i, and x.c;

$Q_x = Q_{x.i} + Q_{x.c}$.

Volumes(ml.):

Note that the volumes are really volumes of distribution of K^{42} as defined by $V_x = \frac{Q_x}{C_x}$.

V_a, V_{vein}, $V_{x.i}$, $V_{x.c}$ = volumes of distribution of K^{42} in a, vein, x.i and x.c.

Rate constants(min^{-1}):

$k_{x.in}$ = rate of exchange of K from x.i to x.c;

$k_{x.out}$ = rate of exchange of K from x.c to x.i.

The rate constants are the reciprocal of the turnover time - that time required for the amount of a substance transferred into or out of a compartment in a steady state to be equal to the amount present in the compartment.

Blood flows(ml/min):

F_{co} = cardiac output of plasma

F_x = flow of plasma through x.

Briefly, Fig. 1 indicates that K^{42} is injected into the venous compartment, is carried by blood flow to the arterial compartment, is further carried through each of four tissue interstitial compartments and returned to the venous compartment. Each interstitial space may give to, or receive from, its corresponding intracellular compartment.

Riggs(26) defines the term, compartment, as follows: "If a substance, S, is present in a biological system in several distinguishable forms or locations, and if S passes from one form or location at a measurable rate, then each form or location constitutes a separate compartment for S."

The choice of compartments is always a simplication of the true physiological system, dictated by what answers are sought, known constants, and limitations of technique for handling too large a number of compartments. Even to say that any compartments with discrete boundaries and volumes exist in an animal may not be strictly true, but it is necessary for this type of analysis. Although the compartments are given names implying exact correspondance to actual anatomic spaces it is important to remember that the correlation is only approximate. In this model the venous and arterial systems are made separate in order to be able to examine the K^{42} concentration in each. Similarly, it would be possible to have separate compartments for inferior and superior body veins, but as this is not useful, it is not done. The ISF and ICF compartments are limited to four each because the system becomes more cumbersome with more and the computer capacity becomes limiting. It would, of course, be more exact to have every tissue represented by a separate compartment since every tissue surely has unique properties in handling K. The tissues were grouped together according to similarities in rate of K^{42} uptake as measured by Walker and Wilde(37).

There is reason to think that the ICF compartments should be subdivided, at least into a free, or relatively easily exchanged K space, and a relatively bound space(3,26). But as no data are available as to the sizes of these intracellular spaces, the K concentrations, or properties of K-exchange, it would be fruitless to include them. The ICF compartments therefore represent a composite of several spaces.

An important necessary assumption at this point is that K^{42} is distributed uniformly throughout each compartment in a short period of time as compared to the length of the experiment. This assumption will be considered for each compartment.

The model assumes that the injected K^{42} is instantaneously equilibrated in V_{vein}, and quickly thereafter in V_a. This is obviously not true--Walker and Wilde(37) show a circulation hump in the arterial plasma at about 45 sec. and 2 min. after injection. However, after 2 min. their arterial curve is smooth. Labelled cells or plasma injected into man finish a rapid mixing phase only after 7-10 min.(23). Readily diffusible ions such as K would be expected to mix faster, and mixing should be faster in the smaller rabbit; nevertheless, some of the rapid initial decline

of Walker and Wilde's arterial time-concentration curve is probably due to plasma mixing.

The mixing of the interstitial compartments is more likely fast and complete since the interstitial space is fed simultaneously from a large capillary surface; however, there are no data to prove this.

The intracellular compartments may equilibrate more slowly; only 75-95% of total human K is exchangeable in 40 hours(7,9,10). The rest would presumably exchange more slowly.

Other assumptions related to the use of a tracer in this model are that the K^{42} injected is treated by the body exactly like K^{39} and that the load is so small as to not disturb the steady state. Also, the half-life of the tracer is long in comparison to the duration of the experiment--K^{42} has a half-life of 12.4hours(16), and no correction for this is made; and there is no excretion--Walker and Wilde found 0.3% of the injected dose in the urine at 2 minutes and 0.6% in the feces.

The next step in the development of the model is a description of the time-concentration curve for each compartment after K^{42} injection. This can best

be done by writing equations for the instantaneous rate of change of concentration for each compartment and then integrating the equations on a computer. Derivations for equations for the 10 compartments in Fig. 1 are given below.

Arterial Compartment

The change in the amount of K^{42} in a equals the amount received from the vein minus the amount lost from a.

$$\frac{dQ_a}{dt} = F_{co}C_{vein} - F_{co}C_a ,$$

$$= F_{co}(C_{vein} - C_a).$$

Assuming V_a is constant(it will be assumed that all volumes remain constant), then

$$V_a\frac{dC_a}{dt} = F_{co}(C_{vein} - C_a) ,$$

$$\frac{dC_a}{dt} = \frac{F_{co}}{V_a}(C_{vein} - C_a).$$

Cellular Compartments

Since the K^{42} is mixed with the normal K which is moving at a constant rate both ways across the cell membrance, the K^{42} is carried at a rate directly proportional to its fraction of total K. Since K^{42} is present in trace amounts, the total K is constant and

and K^{42} exchanges at a rate proportional to the amount present. That is, the transfer of K^{42} from x.i to x.c is proportional to $Q_{x.i}$ and the transfer from x.c to x.i is proportional to $Q_{x.c}$. Therefore

$$\frac{dQ_{x.c}}{dt} = k_{x.in}Q_{x.i} - k_{x.out}Q_{x.c} ,$$

$$\frac{dC_{x.c}}{dt} = k_{x.in}\left(\frac{V_{x.i}}{V_{x.c}}\right) C_{x.i} - k_{x.out}C_{x.c}. \qquad (2)$$

Equation (2) says nothing about the mechanism of transfer across the cell membrane, and it is not valid in a nonsteady state situation.

Interstitial Compartment

The change in amount of K^{42} in the interstitial compartment equals the amount received from the arterial blood flowing to it, and from the associated cells, minus that lost to venous blood and to the cells. Therefore

$$\frac{dQ_{x.i}}{dt} = F_x C_a + k_{x.out}Q_{x.c} - F_x C_{x.vein} - k_{x.in}Q_{x.i},$$

Because $C_{x.vein} \neq C_{vein}$, it is necessary to assume blood is in fast equilibrium with interstitial fluid, so that $C_{x.vein} = C_{x.i}$. Evidence for this is given by theoretical and tracer studies (2,37,40). Then

$$\frac{dQ_{x.i}}{dt} = F_x C_a + k_{x.out}Q_{x.c} - F_x C_{x,i} - k_{x.in}Q_{x.i},$$

$$\frac{dC_{x.i}}{dt} = \frac{F_x}{V_{x.i}}(C_a - C_{x.i}) + k_{x.out}\left(\frac{V_{x.c}}{V_{x.i}}\right)C_{x.c} - k_{x.in}C_{x.i}. \qquad (3)$$

The concentration ratio of K between interstitial fluid and plasma due to the Donnan effect and protein binding is estimated at 0.94 by VanLeeuween(36). The activity coefficient of inorganic ions in interstitial fluid is considered to be .7 to .8(36). Both these factors are ignored in this model.

Venous Compartment

The change in amount of K^{42} in vein equals the sum of the amount gained from each tissue minus that lost to a.

$$\frac{dQ_{vein}}{dt} = \sum_{x=k,m,v,r} F_x C_{x.i} - F_{co}C_{vein},$$

$$\frac{dC_{vein}}{dt} = \frac{F_k}{V_{vein}} \cdot C_{k.i} + \frac{F_v}{V_{vein}} \cdot C_{v.i} + \frac{F_m}{V_{vein}} \cdot C_{m.i} + \frac{F_r}{V_{vein}} \cdot C_r - \frac{F_{co}}{V_{vein}} C_{vein}. \qquad (4)$$

Now the constants in equations(1)-(4) must be estimated. Unfortunately, not many values are available for rabbits, and vlaues for other animals need to be used. $V_{x.i}$ was calculated by (total body wt.) · (tissue fraction of body wt.) · (water fraction of

tissue wt.) · (interstitial fraction of tissue water). 3.5 kg was used as the total body wt. of an average rabbit. Tissue fraction of body wt. was determined directly by Walker and Wilde(37) on their sacrificed rabbits. Water fraction of tissue wt. was taken as 0.61 to 0.78 as quoted for rabbits in (1). $\frac{V_{x.i}}{V_{x.c}}$ was taken as 0.38 as given in (18) for humans; therefore interstitial fraction of tissue water is 0.28. Plasma volume was taken as 3.7% of body wt.(37). Arterial and venous plasma are each arbitrarily assumed to be 50% of total plasma.

Blood flows were computed by (tissue wt.) · (tissue flow/min/wt.) using values from (1) for tissue flow in ml/min/100gm in humans.

Whenever possible the constants were also derived from other sources and by other means for a check of accuracy, and the results were consistent. The only remaining constants are $k_{x.in}$ and $k_{x.out}$. These can be determined with the computer by adjusting the theoretical concentration results to experimental results if the ratio $\frac{k_{x.in}}{k_{x.out}}$ is known. At equilibrium, $\frac{dC}{dt} = 0$, therefore, from equation(2):

$$k_{x.in}\frac{V_{x.i}}{V_{x.c}} C_{x.i} - k_{out}C_{x.c} = 0,$$

$$\frac{k_{x.in}}{k_{x.out}} = \frac{C_{x.c}}{C_{x.i}} \cdot \frac{V_{x.c}}{V_{x.i}},$$

where $C_{x.c}/C_{x.i}$ = 30/1 and $V_{x.c}/V_{x.i}$ = 1/.38 for skeletal muscle(18,38). Therefore $\frac{k_{x.in}}{k_{x.out}} = \frac{30}{.38} = 79.$ This value is used in all tissue compartments.

The constants are summarized in Table 1.

Table 1. Volume and flow constants used in equations (1)-(4) for Fig. 3a,3b.

x	$V_{x.i}$(ml)	F_x(ml/min)	$\frac{F_x}{V_{x.i}}$ (min^{-1})
k	3.6	42.	11.6
v	66.	51.	.778
m	350.	54.	.154
r	75.	36.	.472
Total	494.6	183.	

V_a = 65. ml

V_{vein} = 65. ml

F_{co} = 183. ml

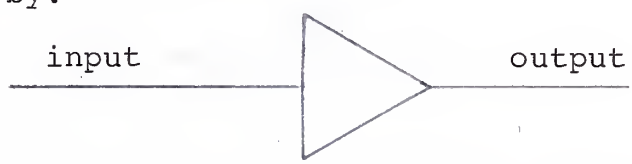
Total ECF volume = 624.6

Total ICF volume = 1301.

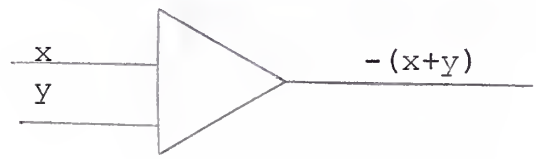
PROGRAMMING THE MODEL

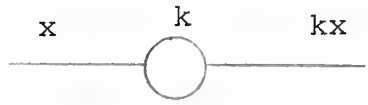
The next step in constructing the model is the solving of the ten simultaneous linear differential equations--equations (1)-(4)--which describe the rate of change of K^{42} for each of the ten compartments of Fig. 1. It is desired to solve for the concentration in any compartment at any time. The analogue computer is peculiarly suited to find this solution. The principles and symbols used will be explained briefly below. For a more complete explanation of the circuits and theory, Strong's, "A Practical Approach to Analogue Computers" is recommended(35).

The computer works by manipulation of voltages. For this model, the voltages represent concentrations of K^{42}. The voltages may be added, multiplied by an adjustable constant or by themselves, and integrated. The basic component is the amplifier, which is represented by:

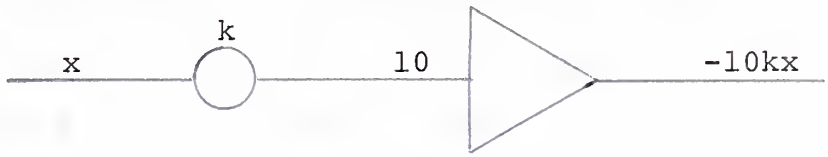


It performs addition of input voltages, and reversal of the sign of the input. E.g.,



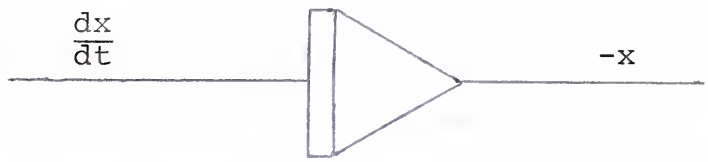
A potentiometer can multiply a voltage by 0 to 1,and is represented by 

. Resistances may be added to an input voltage and serve to multiply by powers of 10. E.g.,



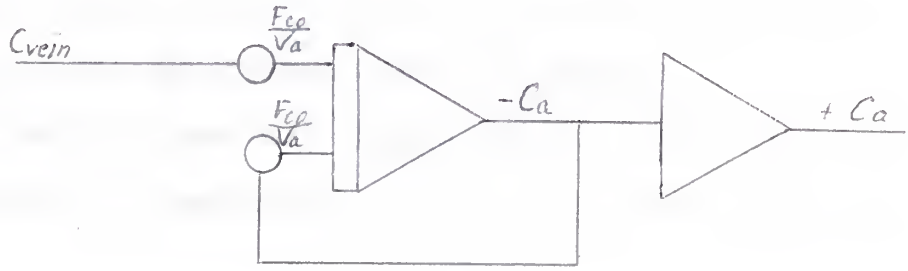
.

An integrator is simply an amplifier with a feedback capacitor; its symbol is:



It has the abilities of an amplifier as well as ability to perform integration of the input voltage with respect to time. An example of how these elements are combined is provided by the program for solution of equation(1), which is restated below, for C_a:

$$\frac{dC_a}{dt} = \frac{F_{co}}{V_a} C_{vein} - \frac{F_{co}}{V_a} C_a$$



The entire program of the model is given in Fig. 2.

The model is now complete with the exception of values for $k_{x.in}$ and $k_{x.out}$. The final values were approached by letting every $k_{x.in}$ be the same, and adjusting them and the corresponding $k_{x.out}$ until the C_a curve approximated Walker and Wilde's arterial time-concentration curve. The closest approximation was with $k_{x.in} = 3.00 min^{-1}$. Next, the total amount in each organ group($C_{x.i}V_{x.i} + C_{x.c}V_{x.c}$) at 2.2minutes was calculated and compared to the values found by Walker and Wilde by sacrificing the rabbits and analyzing the organs. Then $k_{x.in}$ and $k_{x.out}$ were adjusted for each organ to try to better match the experimental quantities. The final values for the rate constants are given in Table 2, with a comparison of model vs physiological data.

Figs. 3a and 3b give all the time concentration curves of the completed model. Figs. 4a, 4b, 5a, 5b, and 6 are drawn from the same computer program, but they have different scales for ease of comparison of concentrations and for observing the concentrations over longer time periods. Potentiometer and resistance settings for all graphs are given in Table 3.

The computer used was a Pace TR-10. The output of any integrator or amplifier can be read at any time on a

digital voltmeter or drawn on a graph. The integration is automatically quickened so that one second of machine time equals one minuted of real time. The accuracy of the amplifiers and integrators is greatest when the output is between 1 and 10 or -1 and -10 volts. This is the reason some of the outputs in Fig. 2 are adjusted to be 10 times the concentration. Each drawn graph was found to be reproducible within less than .05 inch on the vertical or horizontal scale.

The initial conditions are set by putting 10 volts into integrator 14. This represents the initial venous concentration, $C_{vein.0}$, so that 1 volt= 10% $C_{vein.0}$. Until integration is begun, the output of all other integrators is zero. When the integration of all parts is simultaneously begun, C_{vein} falls and the outputs of the other integrators rise as directed by the program and hence by equation (1)-(4).

The model gives all concentration values in $\%C_{vein.0}$. For comparison, Walker and Wilde's curve, which is in P^*(counts/sec/ml of plasma, divided by the number of counts per gram of body wt. injected into the rabbit), was translated into the same units. Their initial concentration was taken from a multiple exponential equation they derived to fit the curve. At time zero, P^* = 27.0

for the entire plasma volume. If the initial amount were distributed only in the venous compartment, as is defined for the model, the concentration would be $P^* = 54.0$. Therefore all his values were changed to $P^*/54 \cdot 100$ which is per cent of initial venous concentration. Because of difficulty in defining the experimental zero point--the point corresponding to instantaneous distribution of K^{42} in the model's venous compartment--the two curves were allowed to match by arbitrarily transposing the experimental points 0.2 minutes to the right. These points are plotted on Fig. 7 and compared with the theoretical time-C_a curve.

DISCUSSION OF THE MODEL

The relative values for the rate constants in Table 2 are: k-210, v-210, m-7.5, and r-1. It did not seem justified to alter the rate constants more, and it may be argued that there is already more than reasonable separation, without experimental work to suggest it. Nevertheless, the theoretical and experimental 2 minute amounts agree poorly for m, r, and plasma. However, compartment m includes skin as well as muscle, whereas Walker and Wilde did not analyze skin; also, as will be shown later, the 2 minute concentrations are highly dependent on blood flow, and

since muscle blood flow is quite variable, a flow variance can explain the discrepancy. The 2 minute C_a agrees well with Walker and Wilde's time-concentration curve, but poorly with their recorded amount of 4.6%, implying perhaps an inconsistency in their work.

It was found while trying different rate constants, that changing $k_{k.in}$, $k_{k.out}$, $k_{v.in}$, $k_{v.out}$, i.e., the rate constants for compartments with high blood flow and quick uptake, altered predominantly the first 2 minutes of the C_a curve. Changing $k_{m.in}$, $k_{m.out}$, $k_{r.in}$, $k_{r.out}$, i.e., the rate constants for the compartments with large volume but slower uptake, altered predominantly the later section of the C_a curve.

Before discussing the results of the model further, it is fitting to examine the validity of the graph as a true representation of the stated hypothesis and for plausibility of the determined rate constants. The total amount in the system should always remain constant. That is, $Q_a + Q_{vein} + \sum_{x=k,v,m,r} Q_x = C_{vein.0}V_{vein} = 6500$ $(\%C_{vein.0})$.

(ml) at any time. This was found to be true on all graphs, partially validating the technique of the graphs, Also, since the model assumes intracellular K concentration is the same in all cells, all $C_{x.c}$'s should approach the

same value, which is (total amount injected)/(total volume of ICF) = (6500 $\%C_{vein.0}$ · ml)/(1300ml) = 5.0 $\%C_{vein.0}$, assuming that no significant amount of K^{42} remains in interstitial spaces. This is seen to be the case in Fig. 6 and Table 4. It is interesting that although 90% of the injected K^{42} is lost from the plasma in the first 2 minutes, final equilibrium is still not attained and is being slowly approached as late as 5 hours after injection.

The steady state inward flux of K is given by $k_{x.in}V_{x.i}C$ where C is the concentration of K in interstitial fluid. If $k_{x.in}$ = 3.00 min^{-1}, $V_{x.i}$ = 21ml per 100 gm. of tissue weight(18) and C = 4meq/l, then K exchange across the cell membrane in either direction = 2.5 x 10^{-3}meq/gm/min. Since $k_{x.in}$ varies in the model from 21 to .1, the theoretical flux varies from 1.75 ·10^{-2} to 2.5 ·10^{-4}meq/gm/min. This approximates the range of values found experimentally(6, 30, 38), as mentioned earlier, although the value for brain of 6.0 x 10^{-5}meq/gm/min(20) is slower even than the 2.5 x 10^{-4} meq/gm/min for compartment r.

In any tracer experiment involving serially placed compartments it is interesting to know which transfer is rate limiting. In this particular model the rate of

uptake of K^{42} in x.c is influenced much more by changes of blood flow than changes of the rate constant. That is, the blood flow is the limiting factor. This is shown by examining the time curve of $C_{v.c}$ with F_v halved and doubled(Fig. 8), as compared to Fig. 3a, 3b, while other flows remain constant, or by multiplying $k_{v.in}$ and $k_{v.out}$ used in Fig. 3a, 3b by 4 and 1/10(Fig. 9). The 2 minute values for Q_v under these different conditions are given in Table 5. Note that the changes in blood flow resulted in marked changes of the $C_{v.c}$ curve as well as the C_a curve and Q_v. $C_{v.i}$ also changes in the expected direction, but does not contribute much to Q_v. The changes in the rate constants, on the other hand, have less effect on all these values. Note that $C_{v.i}$ changes in the opposite direction as $C_{v.c}$ in Fig. 9, and although it contributes only a minor part to Q_v, it does tend to keep Q_v constant when $k_{v.in}$ and $k_{v.out}$ are altered.

Changing the ratio of $\frac{k_{x.in}}{k_{x.out}}$ as would happen if the equilibrium ratio of $\frac{C_{x.i}}{C_{x.c}}$ were changed, has the greatest effect on the organs with fast uptake, as shown in Fig. 10 for $C_{k.i}$ · C_a is not significantly altered.

It is also interesting to compare the time curves of C_a when all blood flows are changed versus when all rate constants are changed(Fig. 11). Here again, the time curve of C_a is more violently altered by blood flow variance than rate constant changes. The same effects could be observed by altering $V_{x.i}$ instead of F_x, since F_x always appears in equations (1)-(4) as part of the ratio $\frac{F_x}{V_{x.i}}$, or $\frac{F_x}{V_{x.i}}$. As the volumes are less variable and easier to determine than flow, it is more relevant to discuss changes in $\frac{F_x}{V_{x.i}}$ in terms of F_x changes.

These observations lead to two conclusions: 1)the theoretical model cannot be used to determine rate constants accurately for different tissues unless the relative blood flows, or more precisely, the ratio $\frac{F_x}{V_{x.i}}$ are well known. The validity of the rate constants which have been found is suspect, since the blood flows and interstitial volumes were estimated with some indeterminable inaccuracy, 2) Walker and Wilde's experiment (37), and similar whole body tracer injection experiments which intended to determine relative organ uptake, have not defined different rates of cellular transfer, but have instead given an index of relative blood flow through

the studied organs. In fact, it has been suggested that K^{42} injection be used for measuring blood flow(29).

The model now suggests better experimental methods of finding rate constants for K exchange across cell membranes. This model, if it is correct, would give good values if each F_x were measured at the time of the experiment and $V_{x.i}$ were known. The model could be simplified to one organ with an isolated, measured blood flow. An easier approach than measuring flow might be to measure $C_{x.vein}$ and thereby $C_{x.i}$ during a tracer experiment. This would be useful from a hepatic vein, renal vein, a vein draining muscle, etc. Figs. 8 and 9 show $C_{x.i}$ is sensitive to changes in rate constants as compared to changes in blood flow in the first 3 minutes. Therefore this would give useful information for determining rate constants even though blood flow was not known with great accuracy.

Still another method is to maintain C_a constant for a single organ, as explained by Conn and Robertson(6). Alternatively, if $C_{x.vein}$ was maintained constant, as by a selfregulated control system, then after the first minute necessary to fill $V_{x.i}$, and before significant K^{42} returned from the cells, the amount put into the artery would be the amount transported into the cells.

SUMMARY AND CONCLUSIONS

An analogue model was devised to quantitatively describe K^{42} kinetics after injection into a whole animal. The model consists of plasma compartments and four tissue interstitial and intracellular compartments. It was used to find rate constants for K exchange across cell membranes in a steady state, and to demonstrate the effect on K^{42} uptake of varying blood flows and rate constants. Whole body tracer experiments examined were found to be inadequate to determine relative or absolute K exchange rates in different tissues because of dependence of K^{42} uptake on blood flow. Alteration in tracer experiments which might allow better determination of exchange rates, were discussed.

The model in its present state is an attempt to quantitate theories of K kinetics. It is too crude an over simplification of the actual system, and the necessary quantitative input is still too inaccurate, to give highly significant output; also, it is limited by not applying in a nonsteady state. Nevertheless, it is hoped the model is able to contribute to the interpretation and planning of experimental work.

In conclusion, models of physiological processes--through the discipline imposed by the quantitative

development--are perhaps most useful to their originators, and are of continued use only when intertwined with experimental approaches. Within these limitations, mathematical models are a powerful aid in physiological research.

Fig. 1. Block Diagram of the Model.

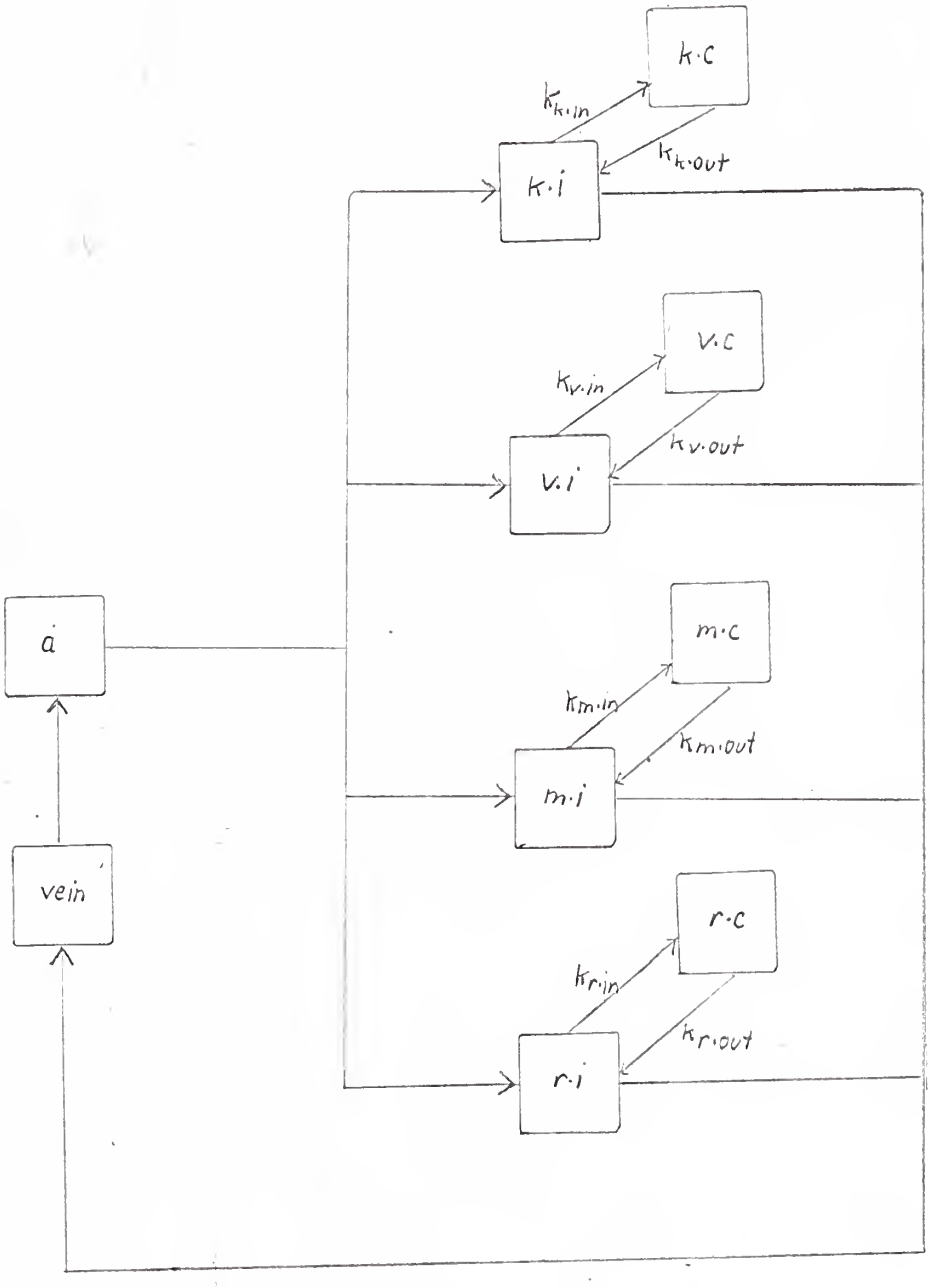


FIG. 2. ANALOG DIAGRAM OF THE MODEL.

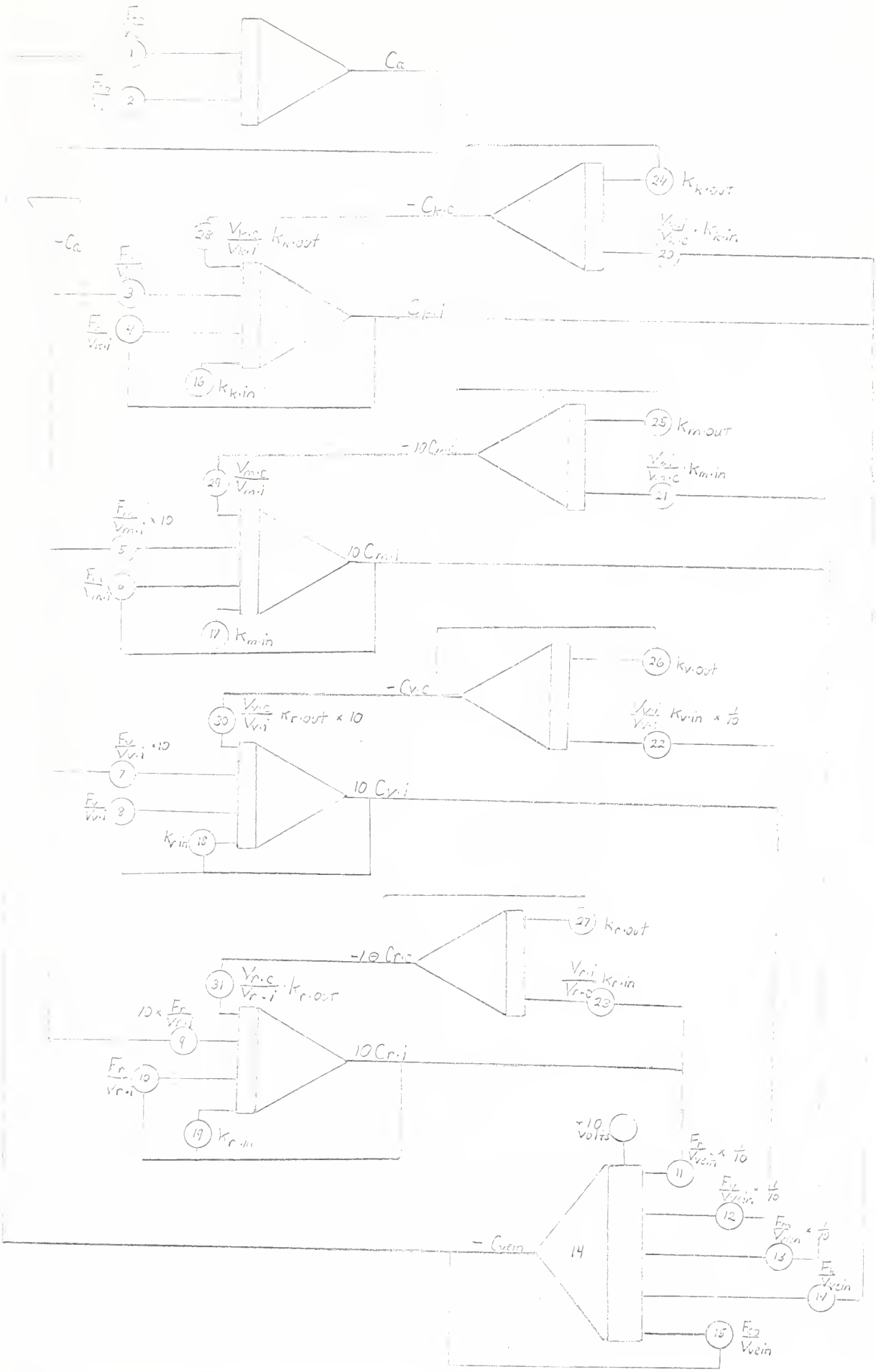


Fig. 3a. Concentration of K^{42} in all interstial and plasma compartments.

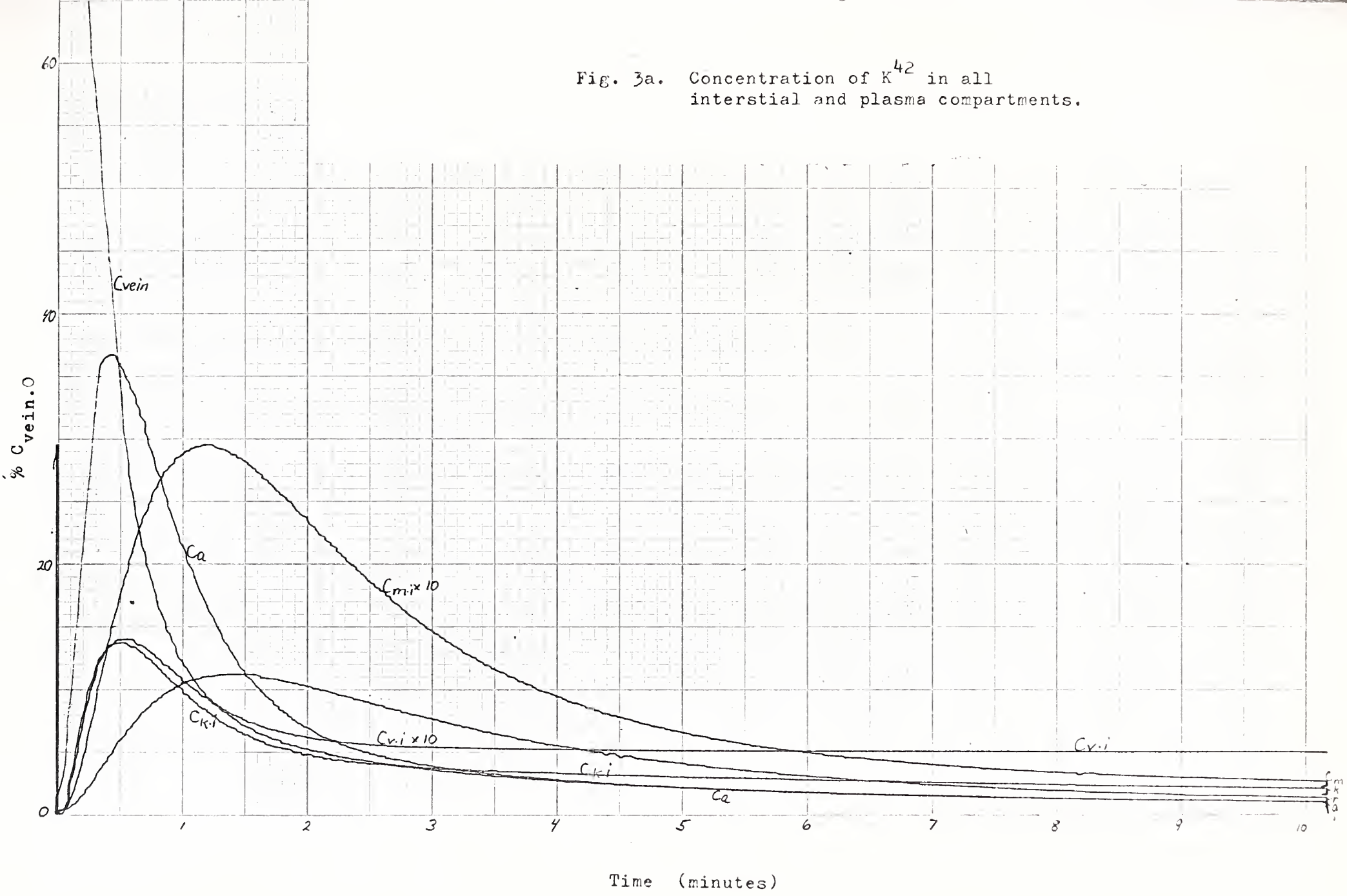
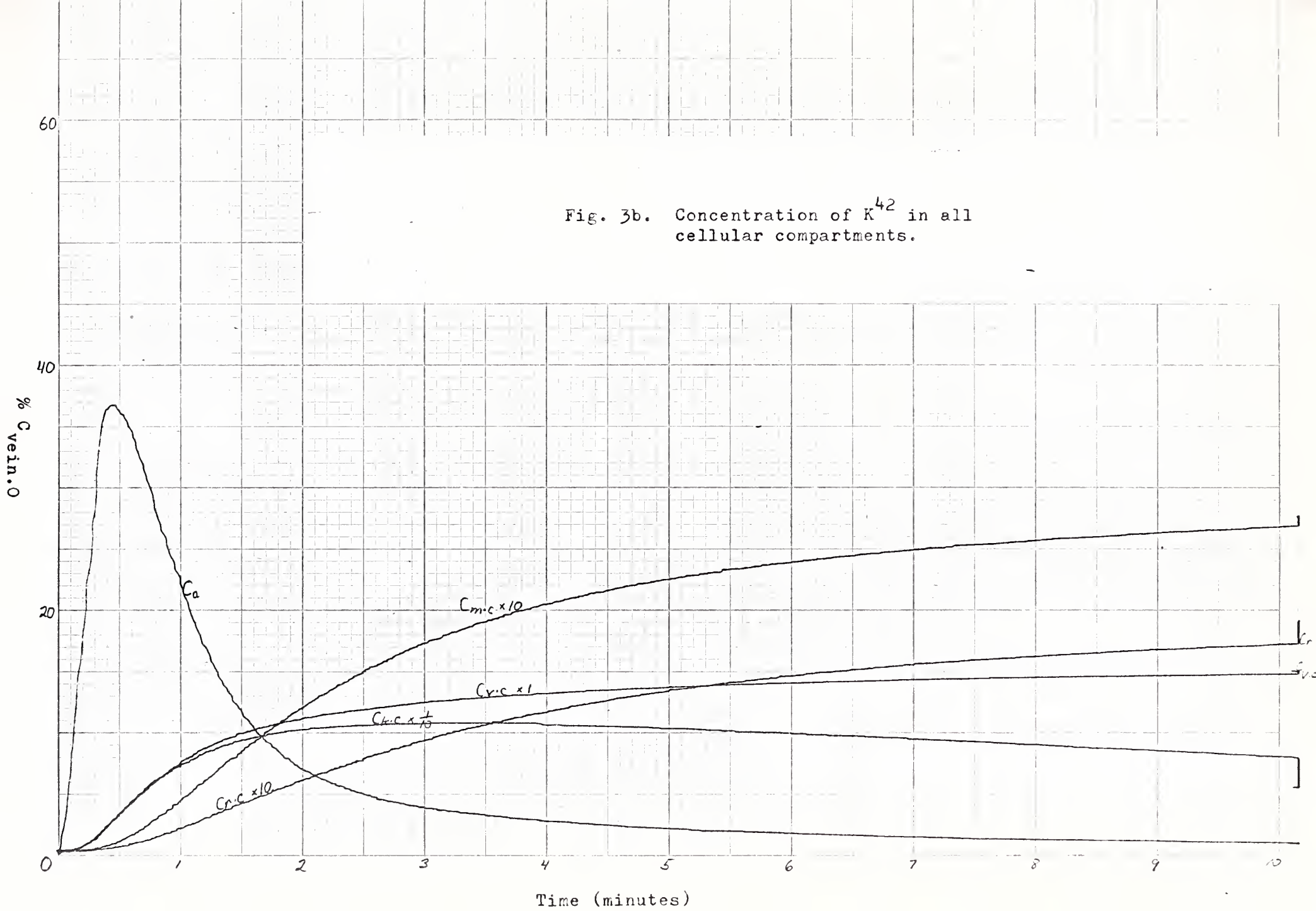


Fig. 3b. Concentration of K^{42} in all cellular compartments.



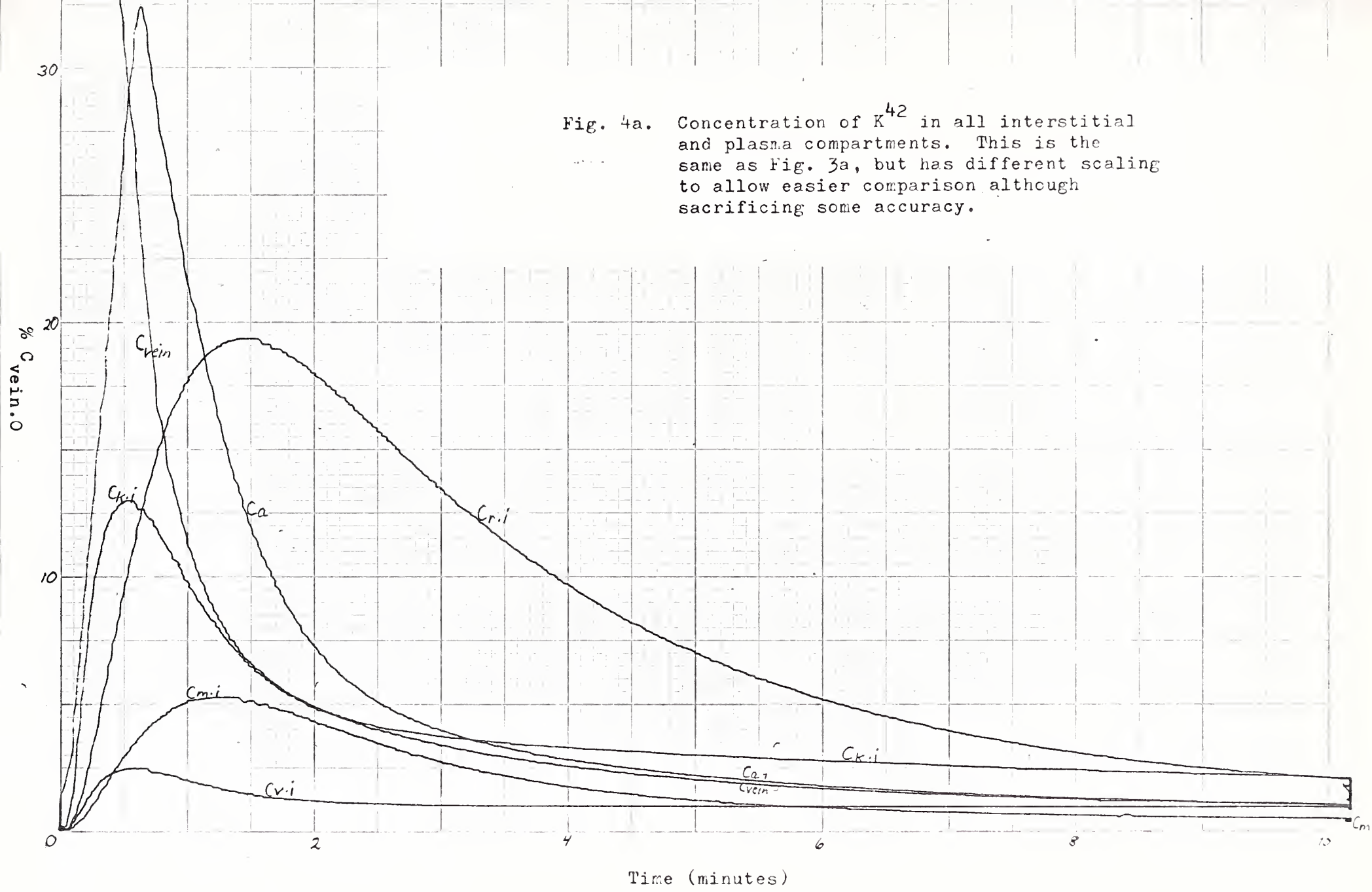


Fig. 4a. Concentration of K^{42} in all interstitial and plasma compartments. This is the same as Fig. 3a, but has different scaling to allow easier comparison although sacrificing some accuracy.

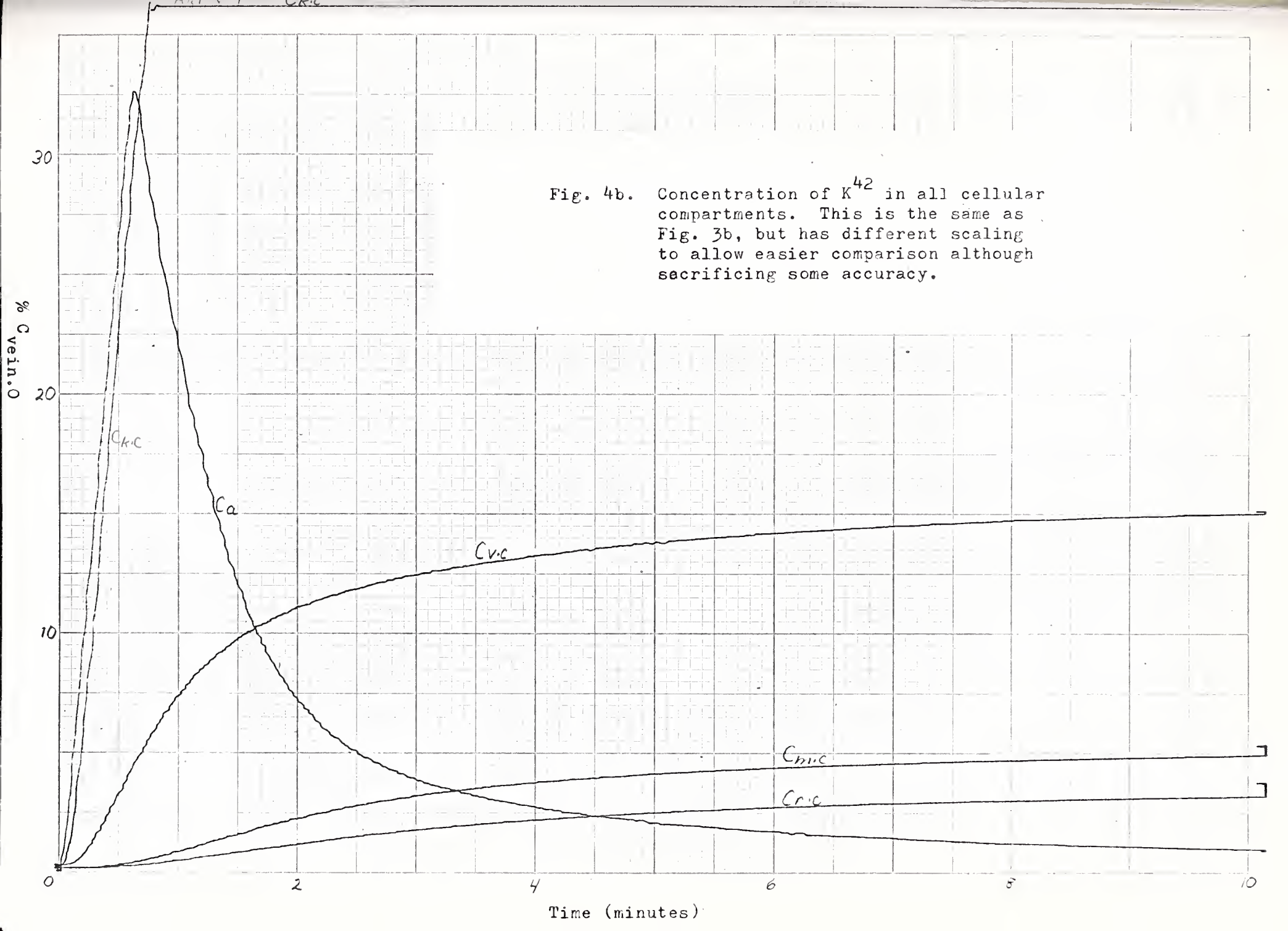


Fig. 4b. Concentration of K^{42} in all cellular compartments. This is the same as Fig. 3b, but has different scaling to allow easier comparison although sacrificing some accuracy.

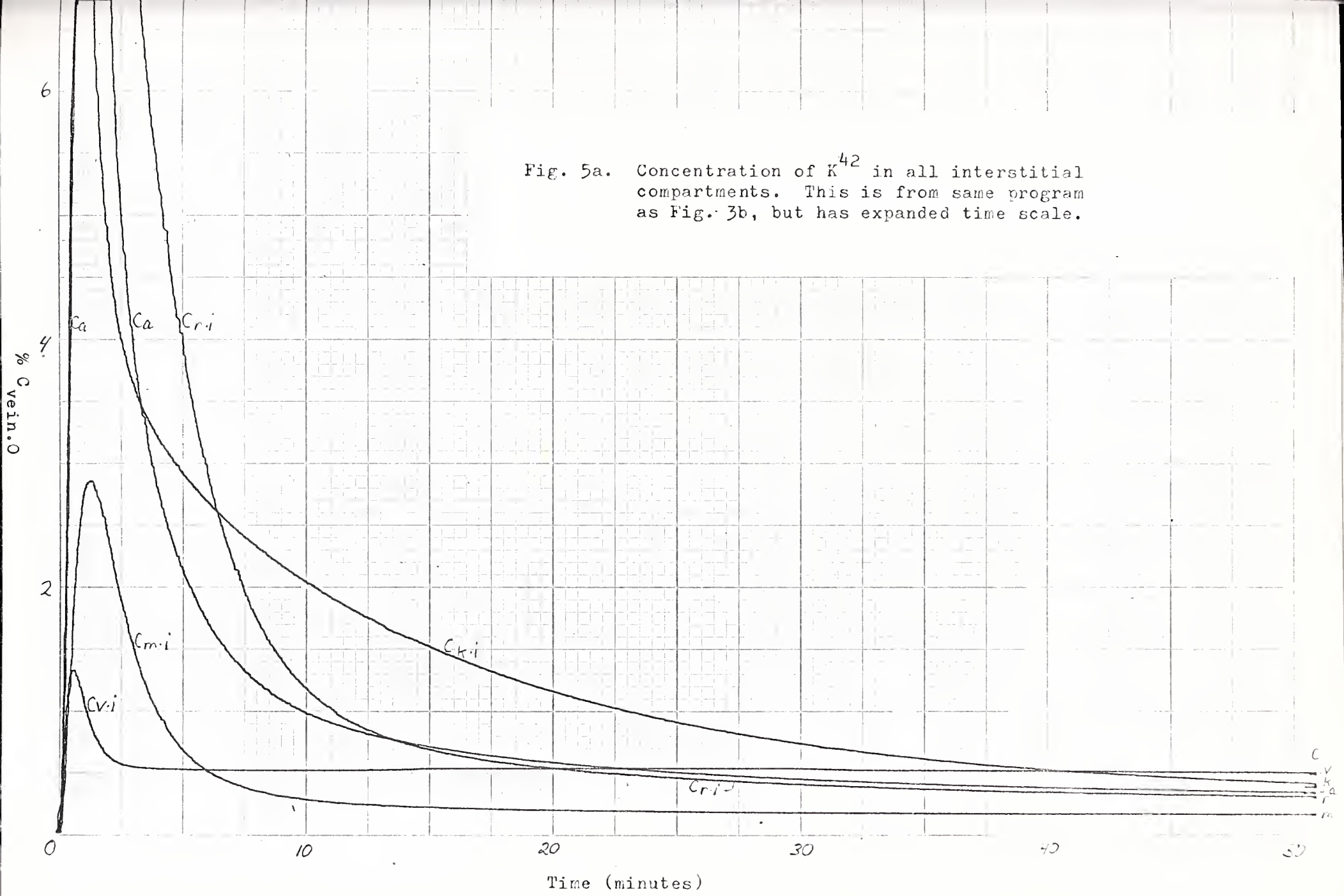


Fig. 5a. Concentration of K^{42} in all interstitial compartments. This is from same program as Fig. 3b, but has expanded time scale.

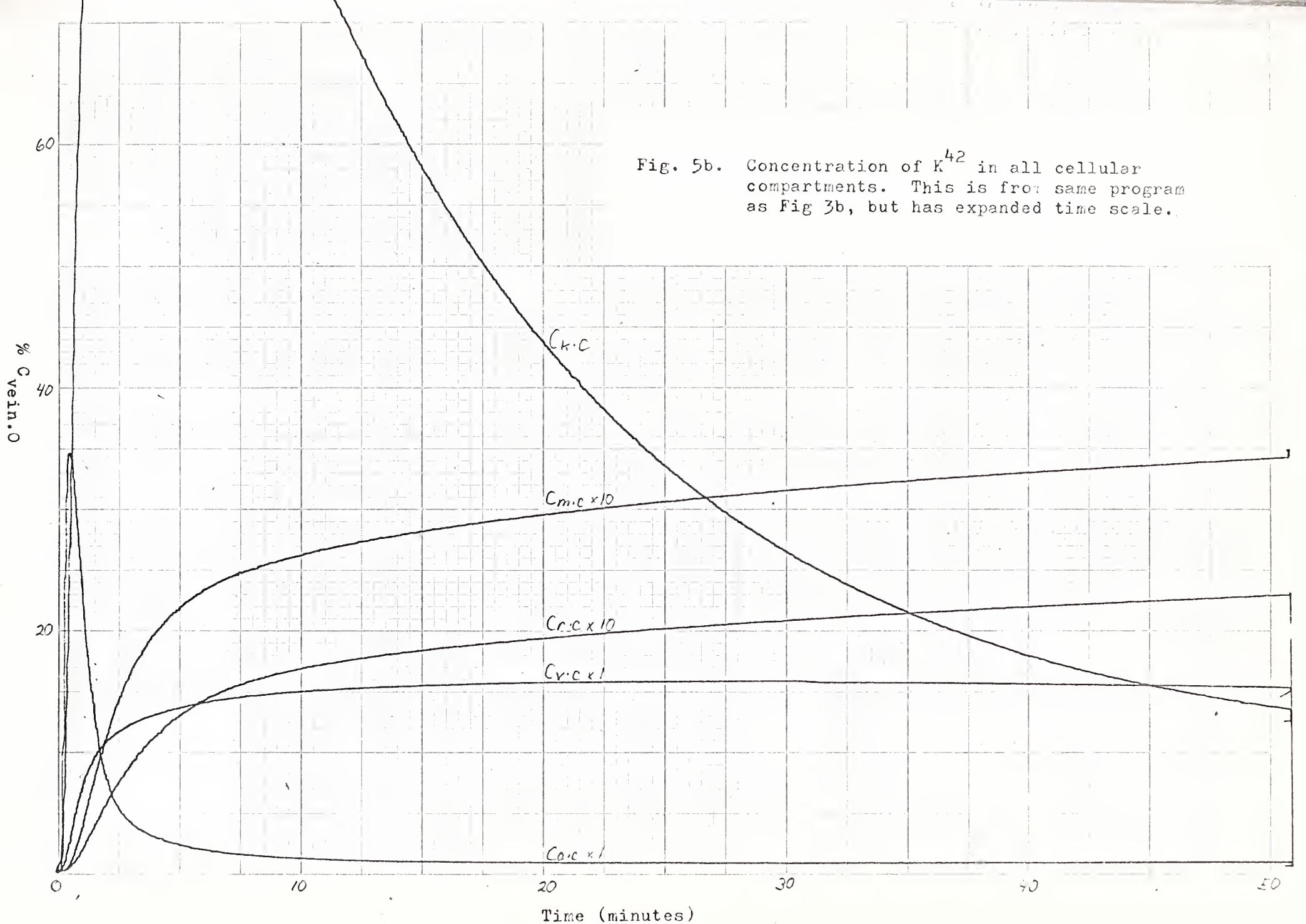


Fig. 5b. Concentration of K^{42} in all cellular compartments. This is from same program as Fig 3b, but has expanded time scale.

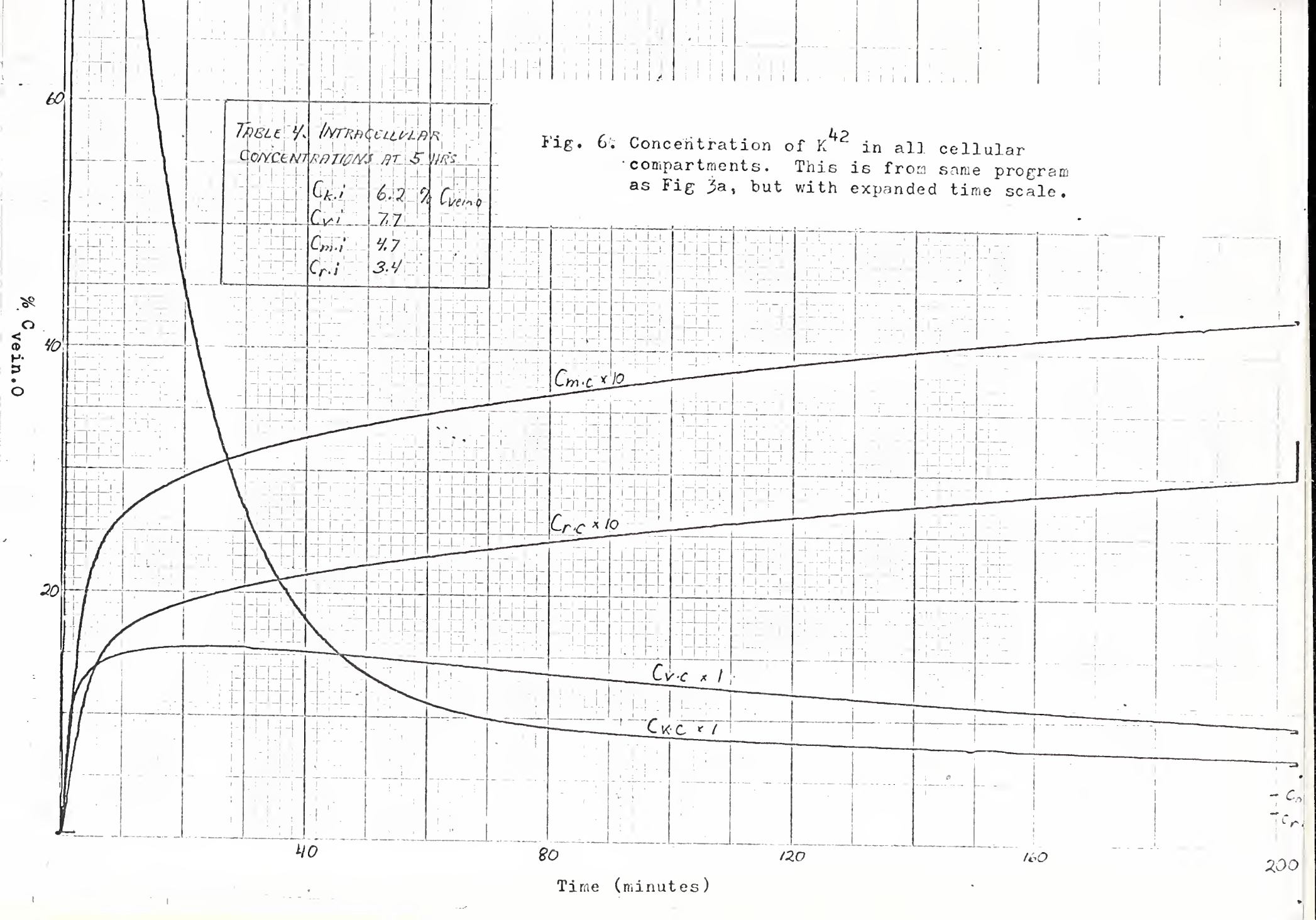


TABLE 4. INTRACELLULAR CONCENTRATIONS AT 5 HRS

$C_{k.i}$	6.2 % $C_{vein.0}$
$C_{v.i}$	7.7
$C_{m.i}$	4.7
$C_{r.i}$	3.4

Fig. 6. Concentration of K^{42} in all cellular compartments. This is from same program as Fig 3a, but with expanded time scale.

Fig. 7. Comparison of theoretical and experimental points(37) for C_a.

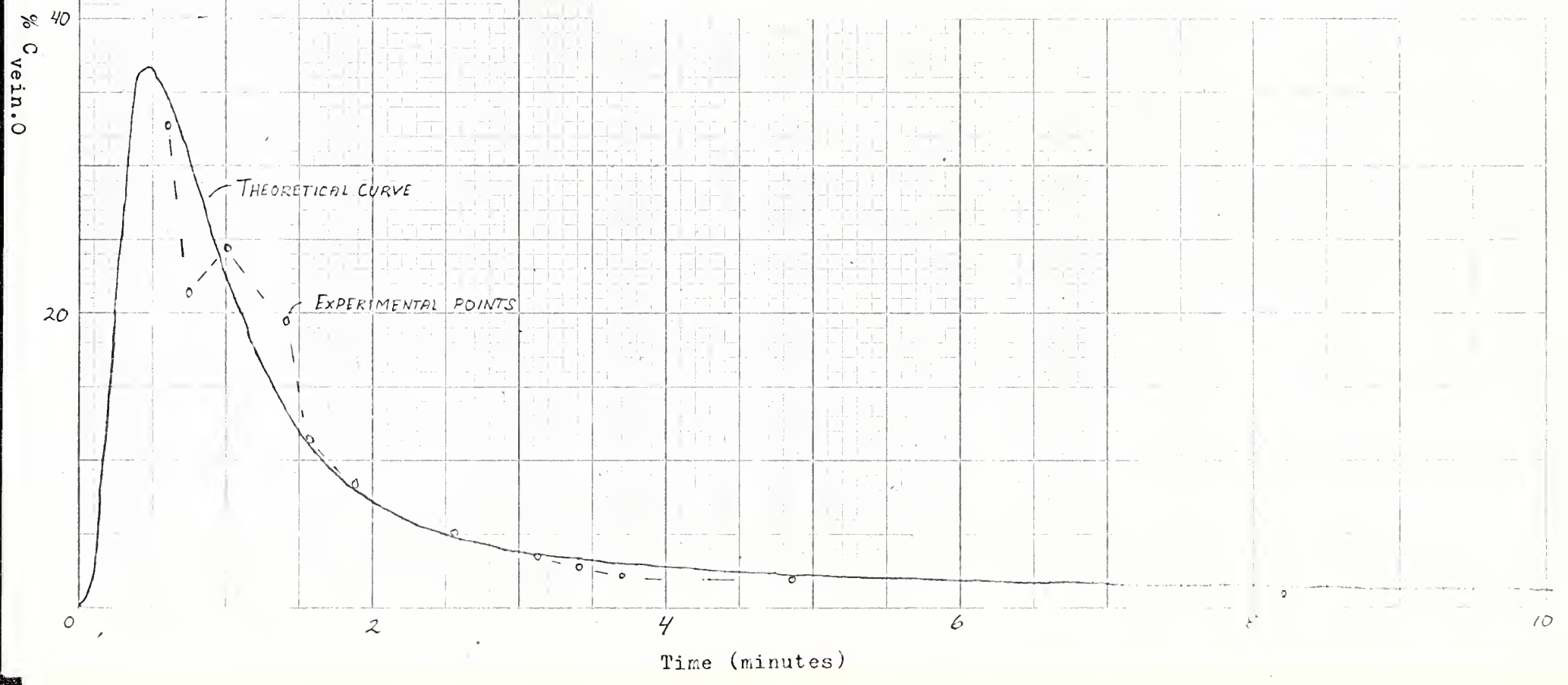
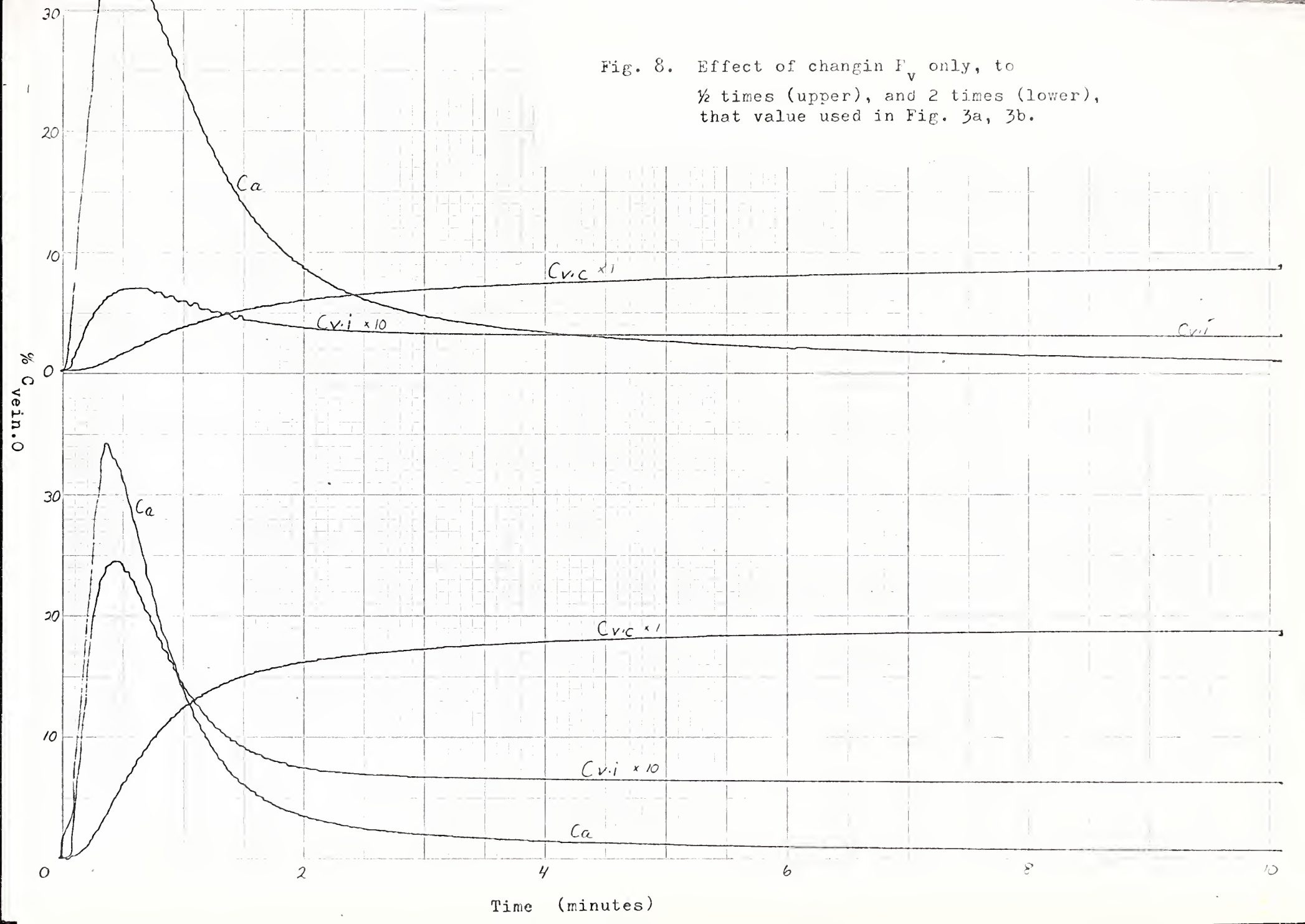


Fig. 8. Effect of changin F_v only, to ½ times (upper), and 2 times (lower), that value used in Fig. 3a, 3b.



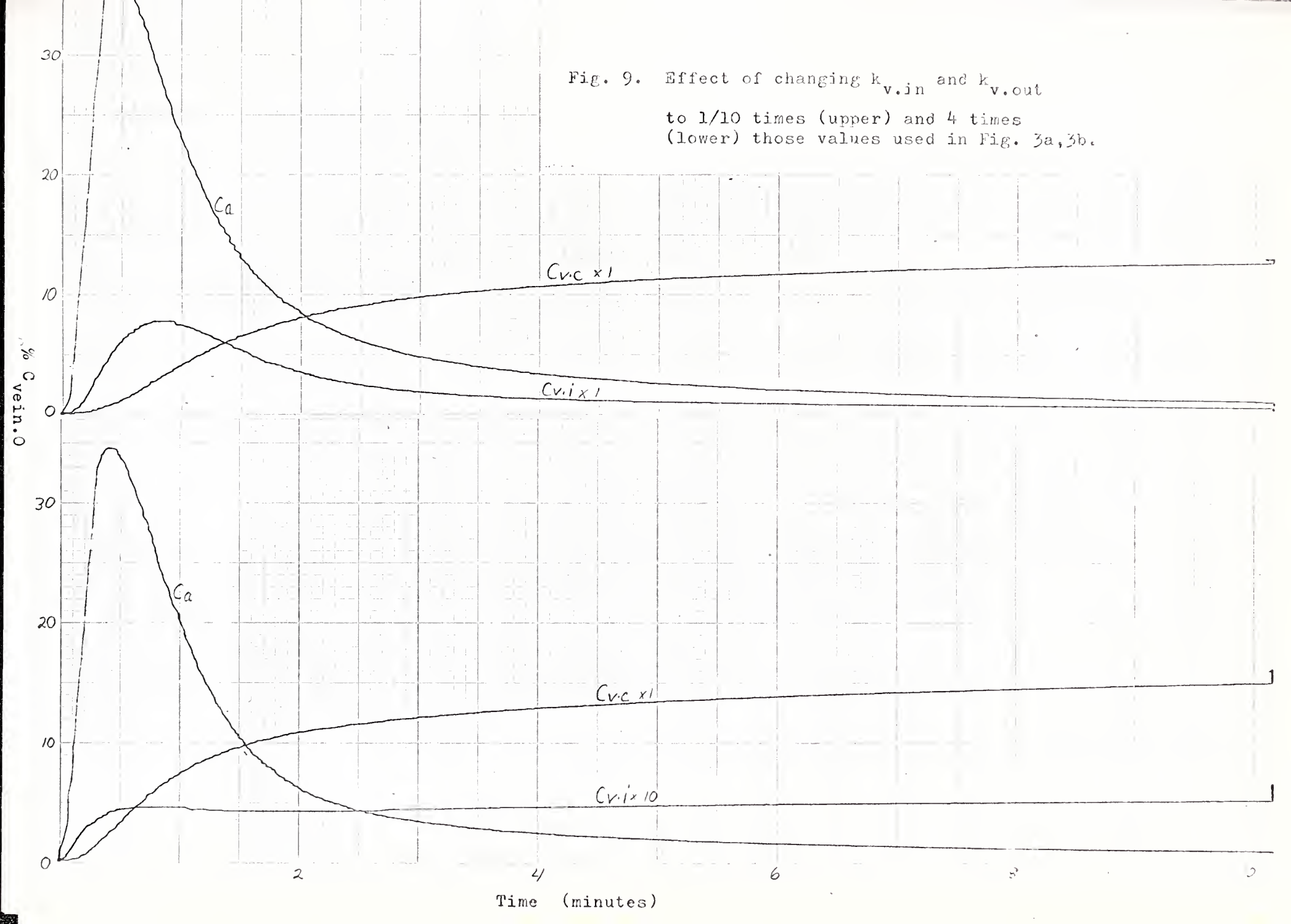


Fig. 9. Effect of changing $k_{v.in}$ and $k_{v.out}$ to 1/10 times (upper) and 4 times (lower) those values used in Fig. 3a,3b.

Fig. 10. Effect of changing the ratio of $k_{x.in}/k_{x.out}$ on C_k.

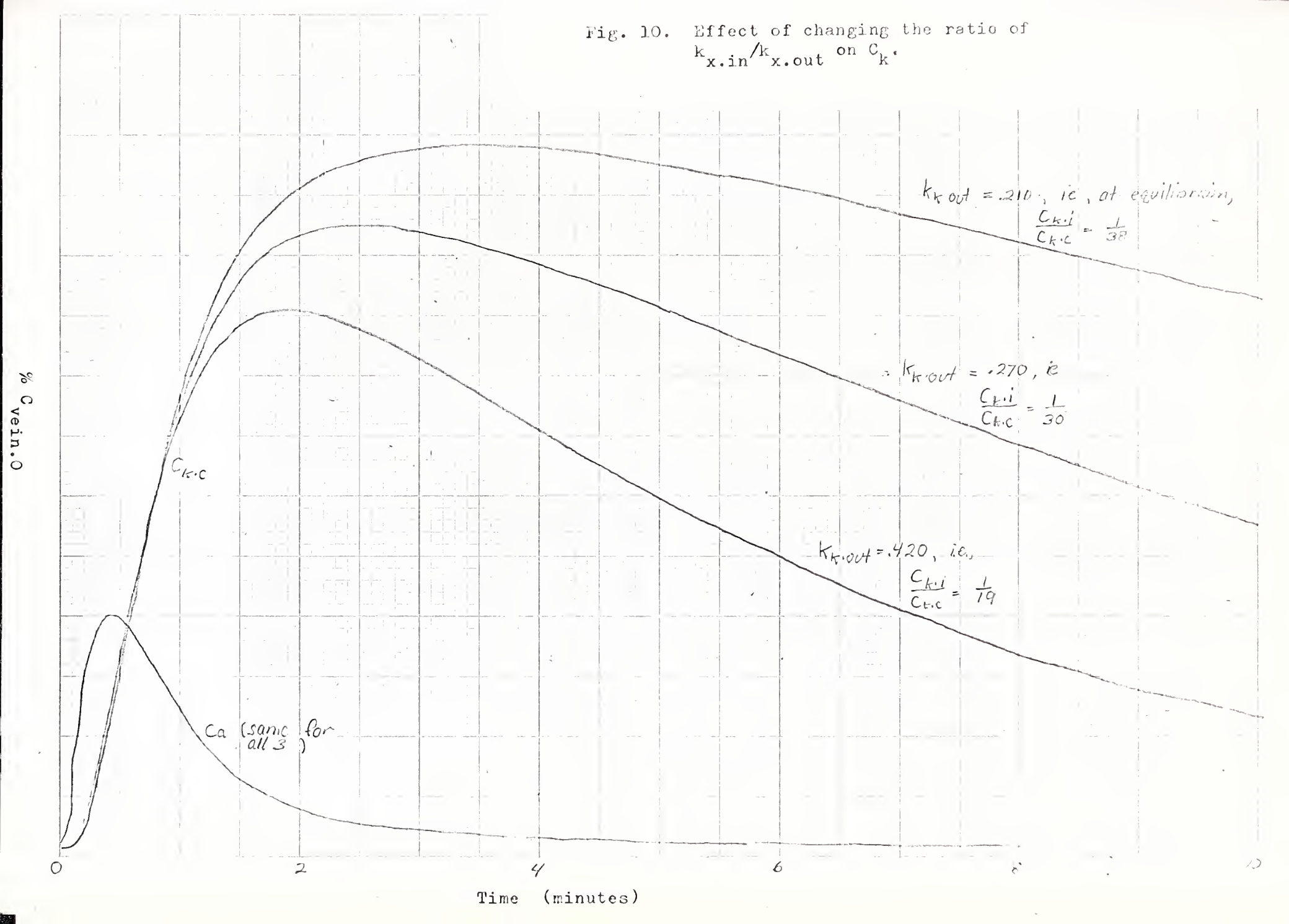


Fig. 11. Comparison of C_a under different conditions.

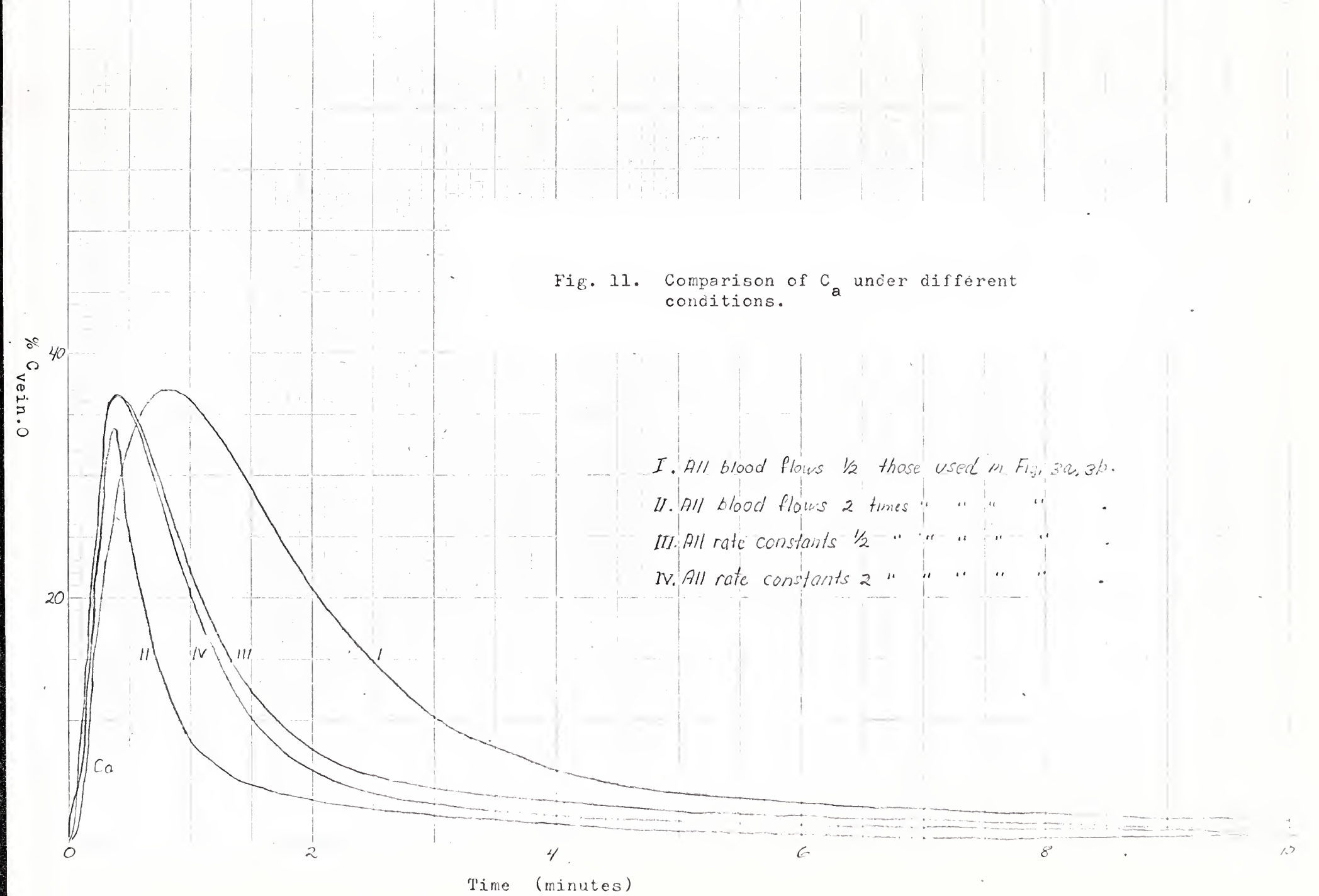


Table 2. Rate constants for Figs. 3a,3b-6.
Comparison of theoretical and experimental K^{42} in tissues, at 2 min. (2.2 min. on graphs).

x	$k_{x.in}$ (min^{-1})	$k_{x.out}$ (min^{-1})	Theoretical totals (% of amount K^{42} injected=$Q_x/6500$	Experimental totals (% of amount K^{42} injected) from (37)
k	21.0	.266	15.0	15.4
v	21.0	.266	30.8	35.3
m	.750	.0095	29.7	11.5[a]
r	.100	.0013	13.6	33.2[b]
a			6.1	4.6
vein			4.8	
Total			100.0	100.0

[a] Includes only muscle.

[b] Includes skin; calculated by subtraction the sum of the other values from 100.0.

Table 3. Potentiometer settings.

Fig.	3a,3b,4a,4b, 5a,5b,6,7,	8		9	
		$F_v x ½$ (upper)	$F_v x 2$ (lower)	$k_{v.in} x 1$ (upper)	$k_{v.in} x 4$ (lower)
		Same values as for Fig. 3a, etc., unless stated.			
Pot.					
1	.282x10	.360x10	.243x10		
2	.282x10	.360x10	.243x10		
3	.116x100				
4	.116x100				
5	.154x10				
6	.154x1				
7	.778x10	.156x100	.389x10		
8	.778x1	.156x10	.389x1		
9	.472x10				
10	.472x1				
11	.549x0.1				
12	.793x0.1	.159x1	.396x0.1		
13	.831x0.1				
14	.646x10				
15	.282x10	.360x10	.243x10		
16	.210x100				
17	.750x1				
18	.210x100			.210x10	.840x100
19	.100x1				
20	.798x10				
21	.285x1				
22	.798x1			.798x0.1	.319x10
23	.379x0.1				
24	.266x1				
25	.095x0.1				
26	.266x1			.266x0.1	.106x10
27	.013x0.1				
28	.700x1				
29	.250x0.1				
30	.700x10			.700x1	.280x100
31	.033xo.1				

Table 5. Compartment v_2 rate constants, plasma flows. and K^{42} quantity at 2.2 min. for all Figures.

Fig.	$k_{v.in}$ (min^{-1})	$k_{v.out}$	F_v (ml/min)	F_{co}	$Q_{v.i}$ (% $C_{vein.}$)	$Q_{v.c}$ .ml)	Q_v
3a,3b,4a, 4b,5a,5b, 6	21.0	.266	51.	183.	40.	1952.	1992
8(upper)	21.0	.266	25.5	157.5	23.	1040.	1063
(lower)	21.0	.266	102.	234.	47.	2820.	2867
9(upper)	2.10	.0266	51.	183	198.	1450.	1648
(lower)	84.0	1.06	51.	183.	28.	1910.*	1938

*This value should be greater that the 1952 for Figs. 3a,3b. The discrepancy can be explained by a small error in the drawing of C_v on the graph. This shows, however, that Q_v does not increase greatly as $k_{v.in}$ increases.

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